

**SUBSTITUTED FURO[2,3-*g*]INDAZOLES
FOR THE TREATMENT OF GLAUCOMA**

BACKGROUND OF THE INVENTION

The present invention relates to the use of substituted furanoindazoles for lowering and controlling normal or elevated intraocular pressure (IOP) and for treating glaucoma.

The disease state referred to as glaucoma is characterized by a permanent loss of visual function due to irreversible damage to the optic nerve. The several morphologically or functionally distinct types of glaucoma are typically characterized by elevated IOP, which is considered to be causally related to the pathological course of the disease. Ocular hypertension is a condition wherein intraocular pressure is elevated but no apparent loss of visual function has occurred; such patients are considered to be at high risk for the eventual development of the visual loss associated with glaucoma. If glaucoma or ocular hypertension is detected early and treated promptly with medications that effectively reduce elevated intraocular pressure, loss of visual function or its progressive deterioration can generally be ameliorated. Drug therapies that have proven to be effective for the reduction of intraocular pressure include both agents that decrease aqueous humor production and agents that increase the outflow facility. Such therapies are in general administered by one of two possible routes, topically (direct application to the eye) or orally.

There are some individuals who do not respond well when treated with certain existing glaucoma therapies. There is, therefore, a need for other topical therapeutic agents that control IOP.

Serotonergic 5-HT_{1A} agonists have been reported as being neuroprotective in animal models and many of these agents have been evaluated for the treatment of acute stroke among other indications. This class of ~~compounds has been mentioned~~ for the treatment of glaucoma (lowering and controlling IOP), see e.g., WO 98/18458 (DeSantis, et al.) and EP 0771563A2 (Mano, et al.). Osborne, et al. (Ophthalmologica, Vol. 210:308-314, 1996) teach that 8-hydroxydipropylaminotetralin (8-OH-DPAT) (a 5-HT_{1A} agonist) reduces IOP in rabbits. Wang, et al. (Current Eye Research, Vol. 16(8):769-775, August 1997, and IVOS, Vol. 39(4),

S488, March, 1998) indicate that 5-methylurapidil, an α_{1A} antagonist and 5-HT_{1A} agonist lowers IOP in the monkey, but attribute the IOP effect to its α_{1A} receptor activity. Also, 5-HT_{1A} antagonists are disclosed as being useful for the treatment of glaucoma (elevated IOP) (e.g., WO 92/0338, McLees). Furthermore, DeSai, et al. (WO 97/35579) and Macor, et al. (U.S. 5,578,612) relate to the use of 5-HT₁ and 5-HT_{1-like} agonists for the treatment of glaucoma (elevated IOP). These anti-migraine compounds, e.g., sumatriptan and naratriptan and related compounds, are 5-HT_{1B,D,E,F} agonists.

It has been found that serotonergic compounds which possess agonist activity at 5-HT₂ receptors effectively lower and control normal and elevated IOP and are useful for treating glaucoma, see commonly owned co-pending application, U.S. Patent Application Serial No. 09/787,332 corresponding to WO 00/16761, both of which are incorporated in their entirety by reference herein. Compounds that act as agonists at 5-HT₂ receptors are well known and have shown a variety of utilities, primarily for disorders or conditions associated with the central nervous system (CNS). U.S. Patent No. 5,494,928 relates to certain 2-(indol-1-yl)-ethylamine derivatives that are 5-HT_{2C} agonists for the treatment of obsessive compulsive disorder and other CNS derived personality disorders. U.S. Patent No. 5,571,833 relates to tryptamine derivatives that are 5-HT₂ agonists for the treatment of portal hypertension and migraine. U.S. Patent No. 5,874,477 relates to a method for treating malaria using 5-HT_{2A/2C} agonists. U.S. Patent No. 5,902,815 relates to the use of 5-HT_{2A} agonists to prevent adverse effects of NMDA receptor hypo-function. WO 98/31354 relates to 5-HT_{2B} agonists for the treatment of depression and other CNS conditions. WO 00/12475 relates to indoline derivatives, and WO 00/12510 and WO 00/44753 relate to certain indole derivatives as 5-HT_{2B} and 5-HT_{2C} receptor agonists for the treatment of a variety of disorders of the central nervous system, but especially for the treatment of obesity. WO 00/35922 relates to certain pyrazino[1,2-a]quinoxaline derivatives as 5-HT_{2C} agonists for the treatment of obsessive compulsive disorder, depression, ~~eating disorders, and~~ other disorders involving the CNS. WO 00/77002 and WO 00/77010 relate to certain substituted tetracyclic pyrido[4,3-*b*]indoles as 5-HT_{2C} agonists with utility for the treatment of central nervous system disorders including obesity, anxiety, depression, sleep disorders, cephalic pain, and social phobias among others. WO 02/40456 and WO 03/00663 relate to certain substituted 1-(pyrazinyl)-piperazines and substituted 1-(pyrimidinyl)-

piperazines, respectively, as agonists or antagonists at 5-HT_{2C} receptors for the treatment of a variety of central nervous system related disorders, especially obesity and sexual dysfunction. Agonist response at the 5-HT_{2A} receptor is reported to be the primary activity responsible for hallucinogenic activity, with some lesser involvement of the 5-HT_{2C} receptor possible
5 [Psychopharmacology, Vol. 121:357, 1995].

Few furan or pyran containing fused indazoles have been reported. The chemical synthesis of 7-methyl- and 1,7-dimethyl-1H-furo[2,3-g]indazole [*Gazz. Chim Ital.* **106**, 1083 (1976)] as well as that of 3-methyl- and 1-(4-aminophenyl)-3-methyl-1H-benzo[*b*]furo[2,3-g]indazole [*An. Asoc. Quim. Argent.* **59**, 69 (1971)] has been reported without discussion of
10 their utility. European Patent Application EP 990,650 (Intl. Publication Number WO 98/56768) relates to substituted 2-(furo[2,3-g]indazol-1-yl)-ethylamines, such as (S)-2-(furo[2,3-g]indazol-1-yl)-1-methylethylamine, which are reported to have high selectivity and affinity for 5-HT_{2C} receptors and are potentially useful for treating a variety of central nervous system disorders. The chemical synthesis of 9-methyl-1H-pyrano[2,3-g]indazol-7-
15 one and the corresponding non-methylated compound was reported [*Indian J. Chem.* **26B**, 436 (1987)] with no mention of utility.

U.S. Patent Nos. 5,561,150 and 5,646,173 relate to certain tricyclic pyrazole derivative compounds which are identified as being 5-HT_{2C} agonists for the treatment of CNS diseases and are primarily directed to lipophilic analogs that have a high probability of entering the
20 brain. Similarly, WO 98/56768 relates to tricyclic 5-HT_{2C} agonists for the treatment of CNS diseases. All the patents and publications mentioned above and throughout are incorporated in their entirety by reference herein.

5-Hydroxytryptamine (serotonin) does not cross the blood-brain barrier and enter the brain. However, in order to increase brain serotonin levels the administration of 5-hydroxy-
25 tryptophan can be employed. The transport of 5-hydroxy-tryptophan into the brain readily occurs, and once in the brain ~~5-hydroxy-tryptophan is rapidly decarboxylated~~ to provide serotonin.

Accordingly, there is a need to provide new compounds which avoid the disadvantages described above and which provide increased chemical stability and a desired length of
30 therapeutic activity, for instance, in decreasing intraocular pressure and treating glaucoma.

SUMMARY OF THE PRESENT INVENTION

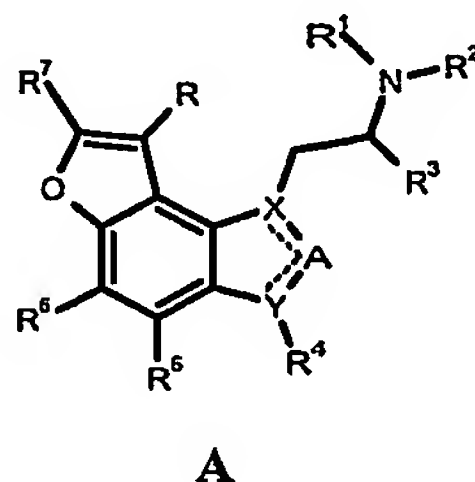
A feature of the present invention is to provide novel compounds which are 5-HT₂ agonists.

Another feature of the present invention is to provide compounds which have increased chemical stability and which are useful in lowering and controlling normal or elevated intraocular pressure and/or treating glaucoma.

Another feature of the present invention is to provide compounds which provide a desired level of therapeutic activity in lowering and controlling normal or elevated intraocular pressure and/or treating glaucoma.

Additional features and advantages of the present invention will be set forth in part in the description that follows, and in part will be apparent from the description, or may be learned by practice of the present invention. The objectives and other advantages of the present invention will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

To achieve these and other advantages, and in accordance with the purposes of the present invention, as embodied and broadly described herein, the present invention relates to a compound having the Formula A:



and described more fully below.

The present invention further relates to pharmaceutical compositions containing at least one compound of Formula A.

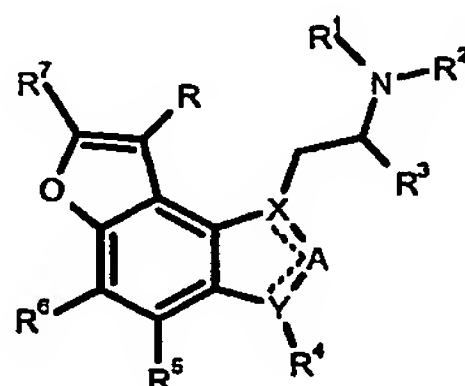
The present invention further relates to methods to lower and/or control normal or elevated intraocular pressure by administering an effective amount of a composition containing a compound having Formula A as described above.

The present invention also relates to a method for treating glaucoma which involves administering an effective amount of a composition containing a compound having Formula I as described above.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are intended to provide a further explanation of the present invention, as claimed.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to a variety of compounds which are useful according to the present invention. These compounds are represented by the following Formula A.



A

Wherein **R**, **R**¹ and **R**² are independently chosen from hydrogen, C₁₋₄alkyl;

R³ is selected from hydrogen, C₁₋₄alkyl; or **R**² and **R**³ can complete a pyrrolidine or piperidine ring, which can be substituted with C₁₋₄alkyl;

R⁴ is hydrogen, halogen, C₁₋₄alkyl;

R⁵ and **R**⁶ are independently chosen from hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfoxide, nitrile, C₁₋₆alkyl substituted with halogen;

R⁷ is chosen from C=OR⁹; S(O)_mR¹⁰; NR¹¹-(C=O)-R¹¹; C₁₋₆alkyl substituted with hydroxyl, C₁₋₆alkoxy, OC(=O)C₁₋₈, CO₂H, CO₂C₁₋₆alkyl, C(=O)NR¹²R¹³, S(O)_mNR¹²R¹³, NR¹⁴R¹⁵,

phenyl or a saturated or unsaturated 5 or 6-membered heterocyclic ring which can contain 1-

4 heteroatoms selected from N, O, or S and can be unsubstituted or substituted with C₁₋₆alkyl, C₁₋₆alkoxy, halogen, haloC₁₋₄alkyl, phenyl or pyridinyl; or R⁷ can be chosen from a heterocyclic ring selected from an oxazole such as oxazol-2-yl, 4,5-dihydro-oxazol-2-yl, or benzoxazol-2-yl, an oxazine such as 5,6-dihydro-[1,3]oxazin-2-yl, a thiazole such as thiazol-2-yl, 4,5-dihydro-thiazol-2-yl, or benzothiazol-2-yl, an imidazole such as imidazol-2-yl, or imidazolidin-2-yl, [1,2,4]oxadiazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]thiadiazol-5-yl, or [1,2,4]thiadiazol-3-yl which can be unsubstituted or substituted with C₁₋₆alkyl, C₁₋₆alkoxy, phenyl or pyridinyl, or C₁₋₆alkyl substituted with phenyl or pyridinyl;

but R⁷ cannot be hydrogen, lower alkyl, hydroxyl, lower alkoxy, amino, mono- or di-loweralkyl amino, lower alkanoylamino, or halogen;

R⁸ is selected from C₁₋₆alkyl, phenyl which can be substituted with C₁₋₆alkyl, C₁₋₆alkoxy, NR¹(C=O)C₁₋₆alkyl, or halogen;

R⁹ is chosen from hydroxyl; C₁₋₆alkoxy; C₁₋₆alkoxy substituted with phenyl or pyridinyl which can be substituted with C₁₋₄alkoxy or halogen; NR¹⁶R¹⁷; C₁₋₆alkyl; or C₁₋₆alkyl substituted with hydroxyl, C₁₋₆alkoxy, NR¹²R¹³, CO₂H, CO₂C₁₋₆alkyl, S(O)_mNR¹²R¹³, halogen, or phenyl or a heterocyclic ring selected from pyrrolidinyl, imidazolyl, morpholinyl, oxazolyl, isoxazolyl, thiazolyl, or tetrazolyl, or pyridinyl which can be unsubstituted or substituted with C₁₋₆alkyl, C₁₋₆alkoxy, halogen, haloC₁₋₄alkyl;

R¹⁰ is chosen from NR¹²R¹³; C₁₋₆alkyl; CH₂phenyl or CH₂pyridinyl which can be substituted with C₁₋₆alkyl, C₁₋₆alkoxy, halogen, or haloC₁₋₄alkyl; or C₂₋₆alkyl substituted with hydroxyl, C₁₋₆alkoxy, NR¹²R¹³, CO₂H, CO₂C₁₋₆alkyl, phenyl, pyridinyl or imidazolyl which can be substituted with C₁₋₆alkyl, C₁₋₆alkoxy, halogen, haloC₁₋₄alkyl;

R¹¹ is NH₂; NR¹R²; C₁₋₆alkyl substituted with hydroxyl, C₁₋₆alkoxy, CO₂H, CO₂C₁₋₆alkyl, phenyl or a saturated or unsaturated 5 or 6-membered heterocyclic ring which can contain 1-4 heteroatoms selected from N, O, or S and can be unsubstituted or substituted with C₁₋₆alkyl, C₁₋₆alkoxy, halogen, haloC₁₋₄alkyl;

R^{12} and R^{13} are independently selected from hydrogen; C_{1-6} alkyl; CH_2Z , where Z is selected from phenyl, pyridinyl, furanyl, thiophenyl, pyrimidinyl, pyrazinyl, or pyridazinyl, and which can be substituted with C_{1-6} alkyl, C_{1-6} alkoxy, halogen, or halo C_{1-4} alkyl; C_{2-6} alkyl substituted with hydroxyl, C_{1-6} alkoxy, CO_2H , CO_2C_{1-6} alkyl, NR^1COC_{1-6} alkyl, or halogen; or
5 R^{12} , R^{13} , and the intervening nitrogen atom can form a heterocyclic ring selected from morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, azetidine, pyrrolidine, piperidine, piperazine, unsubstituted or substituted with C_{1-4} alkyl or C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy or halogen;

R^{14} and R^{15} are independently selected from hydrogen, C_{1-6} alkyl, hydroxyl, C_{1-6} alkoxy,
10 $(C=O)-R^{11}$, $S(O)_mR^8$, phenyl or pyridinyl which can be substituted with C_{1-6} alkyl, C_{1-6} alkoxy, halogen, or halo C_{1-4} alkyl; or R^{14} , R^{15} and the nitrogen atom to which they are attached can form a heterocyclic ring selected from pyrrolidine, piperazine, or piperidine, which can be substituted with C_{1-6} alkyl, phenyl, or pyridinyl;

R^{16} and R^{17} are independently selected from hydrogen; C_{1-6} alkyl; hydroxyl; C_{1-6} alkoxy;
15 CH_2Z , where Z is selected from phenyl, pyridinyl, furanyl, thiophenyl, pyrimidinyl, pyrazinyl, or pyridazinyl, and which can be substituted with C_{1-6} alkyl, C_{1-6} alkoxy, halogen, or halo C_{1-4} alkyl; C_{2-6} alkyl substituted with hydroxyl, C_{1-6} alkoxy, halogen, $NR^1(C=O)C_{1-6}$ alkyl, or a phenyl or a heterocyclic ring selected from a pyrrole, such as pyrrolidin-2-yl, an imidazole such as imidazo-2-yl or imidazo-4-yl, a morpholine such as
20 morpholin-3-yl, a piperidine such as piperidin-4-yl, oxazolyl, isoxazolyl, thiazolyl, tetrazolyl, pyridinyl, which can be unsubstituted or substituted with C_{1-6} alkyl, C_{1-6} alkoxy, halogen, halo C_{1-4} alkyl, phenyl C_{1-4} alkyl, oxo ($=O$); or R^{16} , R^{17} , and the intervening nitrogen atom can form a heterocyclic ring selected from morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, azetidine, pyrrolidine, piperidine,
25 piperazine, unsubstituted or substituted with C_{1-4} alkyl or C_{1-4} alkyl substituted with hydroxy, oxo ($=O$), C_{1-4} alkoxy, or phenyl;

m is 0 – 2;

A is N or CH; and

X and Y are either N or C, wherein X and Y cannot be the same; and the dashed bonds denote a suitably appointed single and double bond.

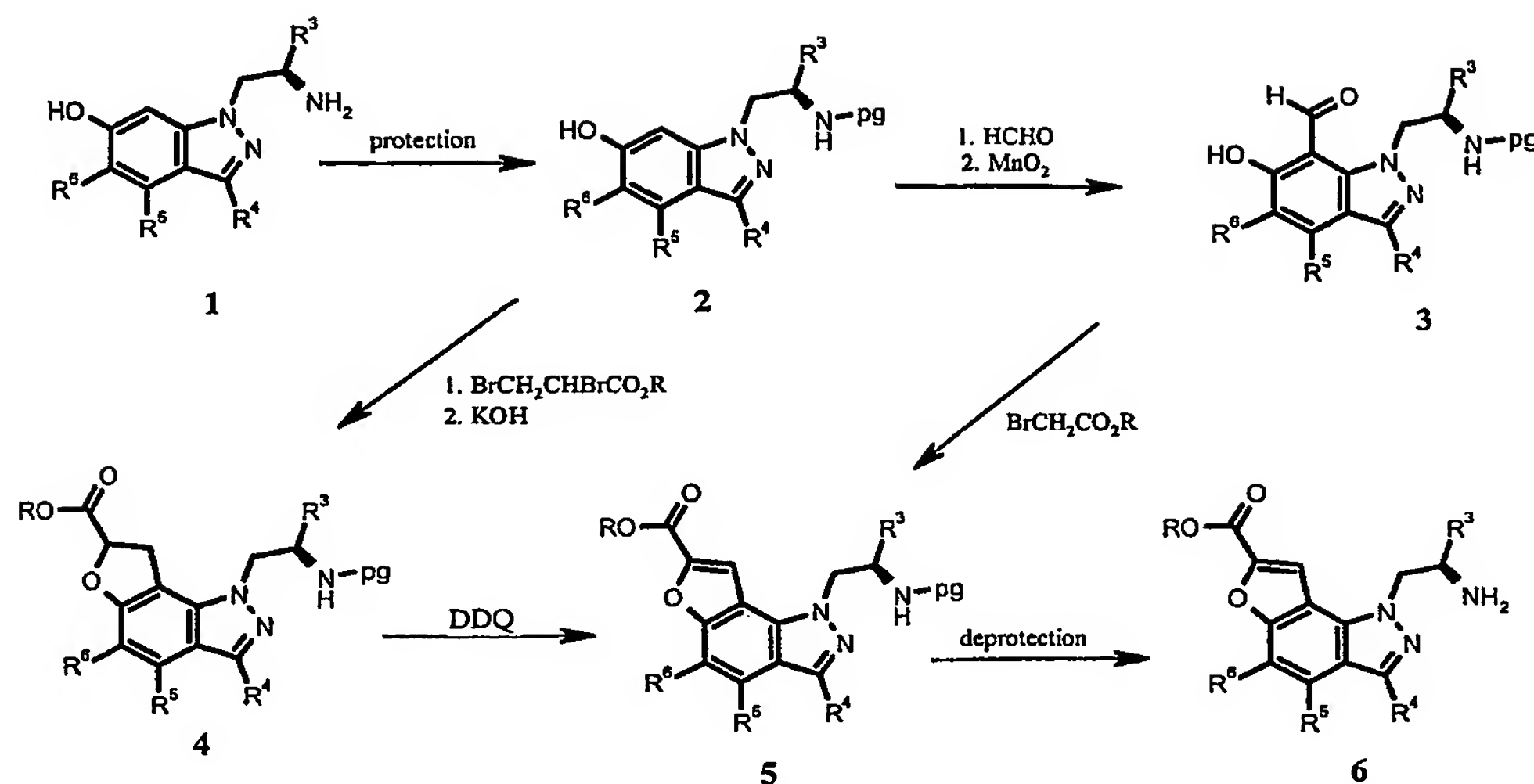
In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C_{i-j} prefix where the numbers i and j define the number of carbon atoms. This definition includes straight chain, branched chain, and cyclic alkyl or (cyclic alkyl)alkyl groups. A substituent may be present either singly or multiply when incorporated into the indicated structural unit. For example, the substituent halogen, which means fluorine, chlorine, bromine, or iodine, would indicate that the unit to which it is attached may be substituted with one or more halogen atoms, which may be the same or different.

SYNTHESIS

Compounds of Formula A can be prepared by using one of several synthetic procedures.

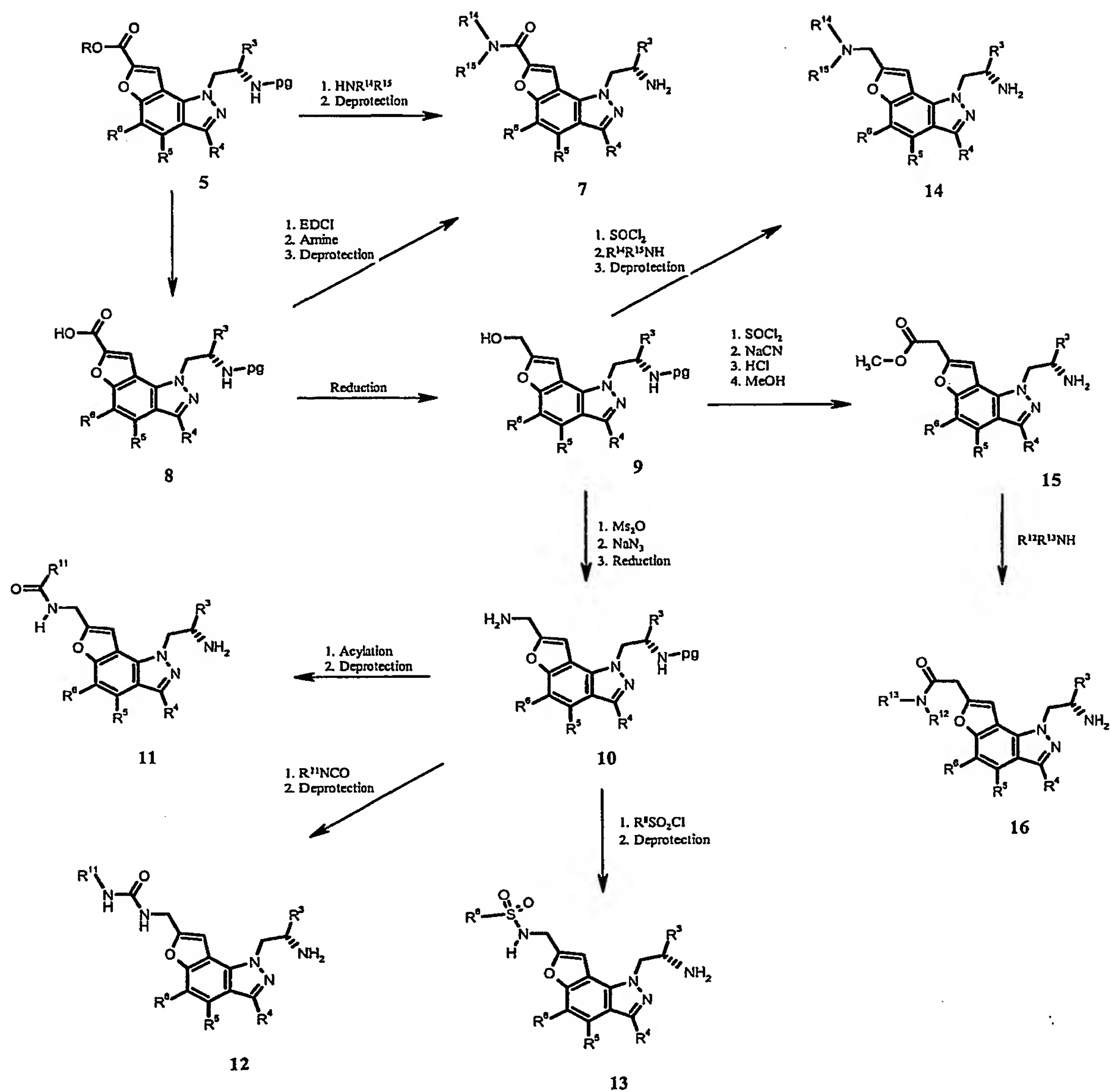
For example, esters of 1-(2-aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid can be prepared from an appropriately protected 1-(2-aminopropyl)-1*H*-furo[2,3-*g*]indazol-6-ol (1) either via the dihydrofuran intermediate 4 [Helv. Chim. Acta, 84:2198 (2001)] or by way of the 7-formyl intermediate 3 as outlined in Scheme 1. As used herein, Pg denotes a suitable protective group to assure that a particular atom is not modified during the indicated chemical reaction. See, for example, the use of carbobenzyloxy in the Examples below.

Scheme 1

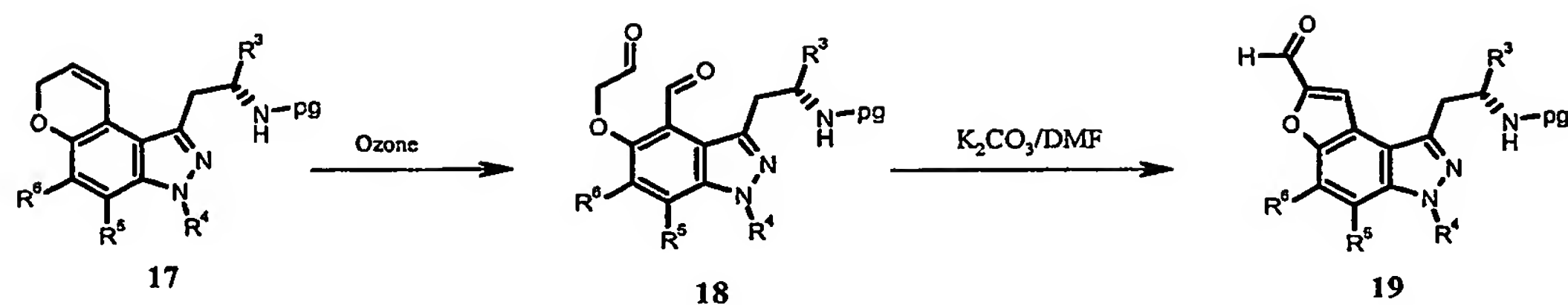


As described below, other compounds of Formula A can be prepared from the appropriately
 5 *N*-protected ester intermediates **5** through select functional group transformations well-known in the art. For example, reaction of certain esters **5** with the desired primary or secondary amine or ammonia followed by deprotection will provide the desired 7-carboxamide compounds **7** of Formula A. Alternatively, it may be preferable to initially hydrolyze an ester **5** to the corresponding carboxylic acid **8**, which can be suitably activated,
 10 such as with an appropriated carbodiimide reagent, and then reacted with the desired amine to give, after deprotection, the desired 7-carboxamides. Yet other compounds of Formula A can be prepared by initially reducing the intermediate ester or acid to the corresponding 7-hydroxymethyl intermediate **9**, which can subsequently be activated, such as by formation of an appropriate sulfonate ester, followed by reaction with a desirable nucleophile and
 15 suitable deprotection as outlined in Scheme 2.

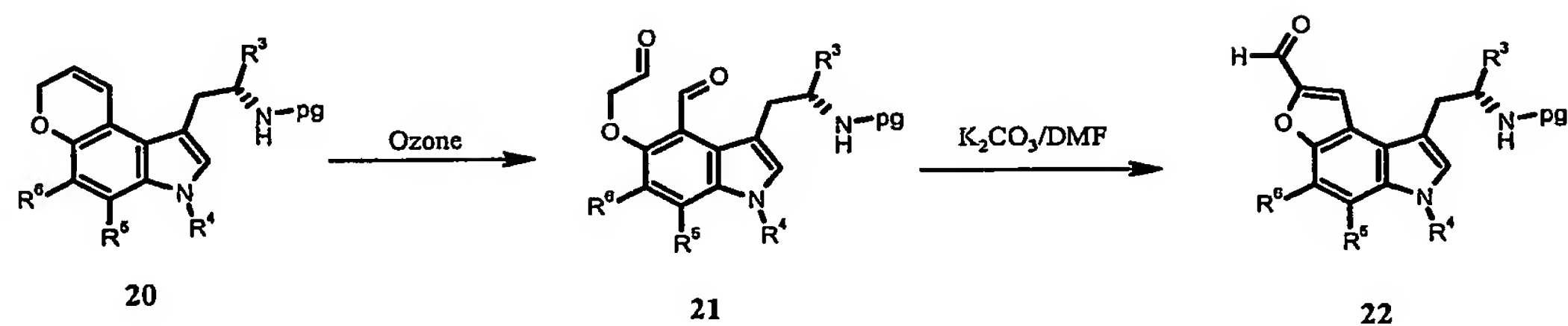
Scheme 2:



Scheme 3



Scheme 4



Using the procedures described in Schemes 1-4 (above), the Examples 1-20 (below), and well known procedures, one skilled in the art can prepare the compounds disclosed herein.

The following examples are given to illustrate the preparation of compounds that are the subject of this invention but should not be construed as implying any limitations to the claims. The preparation of preferred compounds of Formula A is described in Examples 3, 4, 10 and 11, with Examples 4 and 11 describing the preparation of the most preferred compounds. The proton magnetic resonance spectrum of each compound of the Examples was consistent with the assigned structure.

Example 1

1-((S)-2-Aminopropyl)-1H-furo[2,3-g]indazole-7-carboxylic acid ethyl ester fumarate

Step A: [(S)-2-(6-Hydroxy-indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

1-((S)-2-Aminopropyl)-1*H*-indazol-6-ol [prepared in accordance with commonly owned WO 02/098862A1, the contents of which are by this reference incorporated herein] (2.00 g, 10.5 mmol) was suspended in THF (20 mL) and saturated aqueous sodium bicarbonate (10 mL) and benzyl chloroformate (1.50 mL, 15 mol) were added. The mixture was stirred at room temperature until the starting amine dissolved. Saturated aqueous sodium bicarbonate (150 mL) was added and the reaction mixture extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried (magnesium sulfate), filtered, and evaporated to give a tan foam (2.65 g, 78%) which was pure by LC/MS (+APCI) *m/z* 326 (*M* + *H*⁺).

Step B: [(S)-2-(6-Hydroxy-7-hydroxymethyl-indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester To a stirred solution of the product from Step A (2.2 g, 6.8 mol) in THF (30 mL) was added potassium hydroxide (3.3%, 5 mL) and aqueous formaldehyde (37%, 1.6 mL); this solution was heated at 55 °C for 2 h followed by stirring for an additional 18 h at room temperature. A saturated ammonium chloride solution (30 mL) was added to the reaction mixture, which was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine (30 mL), dried and evaporated. The residue was purified by chromatography (silica, 50% ethyl acetate in hexane) to give 6 as an oil (2.2 g, 91%): ¹H NMR δ (DMSO-*d*₆) δ 7.87 (s, 1H), 7.46 (d, 1H, *J* = 8.5 Hz), 7.32 (m, 5H), 6.78 (d, 1H, *J* = 8.5 Hz), 6.50 (d, 1H, *J* = 7.8 Hz), 4.78 (s, 2H), 4.68-4.48 (m), 1.03 (d, 3H, *J* = 6.0 Hz); MS (ES) *m/z* 356 (*M*⁺).

Step C: [(S)-2-(7-Formyl-6-hydroxy-indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

To a stirred solution of the product from Step B (0.75 g, 2.11 mmol) in tetrahydrofuran (10 mL) was added activated manganese dioxide (0.75 g) and the resultant solution was stirred for 18 h at 45 °C. The solution was filtered through a filter aid and the filtrate was evaporated. The residue was purified by chromatography (silica, 30% ethyl acetate in hexane) to yield a solid (0.54, 72%): mp 135-137 °C; MS (ES) *m/z* 254(*M*⁺); ¹H NMR (CDCl₃) δ 13.18 (s, 1H), 10.77 (s, 1H), 7.90 (s, 1H), 7.57 (d, 1H, *J* = 8.0 Hz), 7.33-7.27 (m,

5H), 6.81 (d, 1H, $J = 8.0$ Hz), 5.05 (m, 3H), 4.70 (m, 1H), 4.52-4.47 (m, 1H), 4.23-4.19 (m, 1H), 1.22 (d, 3H, $J = 8.0$ Hz).

Step D: 1-((S)-2-Benzoyloxycarbonylaminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid ethyl ester

To a stirred solution of the product from Step C (0.20 g, 0.56 mmol) in DMF (10 mL) was added potassium carbonate (0.23 g, 1.68 mmol) followed by ethyl 2-bromoacetate (0.07 mL, 0.62 mmol) at room temperature and the resultant solution was heated at 70°C for 20 h. Saturated aqueous ammonium chloride (20 mL) was added followed by ethyl acetate (50 mL). The organic layer was separated and the aqueous was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried and evaporated. The residue was purified by chromatography (silica, 50% ethyl acetate in hexane) to give an oil (0.10 g, 42%): MS(ES) m/z 422 (M^+); 1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 8.05 (s, 1H), 7.72 (d, 1H, $J = 8.8$ Hz), 7.43 (d, 1H, $J = 8.8$ Hz), 7.33 (m, 5H), 5.05-5.09 (m, 2H), 4.58 (m, 1H), 4.30 (m, 2H), 1.45 (t, 3H, $J = 7.2$ Hz), 1.17 (d, 3H, $J = 6.8$ Hz).

Step E: 1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid ethyl ester fumarate

To a solution of the product from Step D (0.10 g, 0.24 mmol) in ethanol (5 mL) under nitrogen was added Pd/C (10%, 0.01 g) and the suspension was stirred under a hydrogen atmosphere at room temperature for 18 h. The solution was filtered through a filter aid and the filtrate was concentrated to a residue, which was purified by chromatography (silica, dichloromethane, 10% methanol in dichloromethane and 15% methanol in dichloromethane) to give a syrup (0.06 g, 88%). The syrup was dissolved in methanol and combined with a solution of fumaric acid (0.02 g) in methanol (1.0 mL). Evaporation of this mixture provided a residue that solidified from a mixture of methanol and ethyl acetate (0.06 g): mp 184-185 °C; MS (ES) m/z 288 (M^+); 1H NMR ($DMSO-d_6$) δ 8.46 (s, 1H), 8.28 (s, 1H), 7.93 (d, 1H, $J = 8.8$ Hz), 7.55 (d, 1H, $J = 8.8$ Hz), 6.55 (s, 3H), 4.84-4.89 (m, 2H), 4.42 (q, 2H, $J = 7.2$ Hz), 3.72 (m, 1H), 1.37 (t, 7H, $J = 7.2$ Hz), 1.14 (d, 3H, $J = 6.4$ Hz); Analysis. Calculated for

$C_{15}H_{17}N_3O_3 \cdot 1.5 C_4H_4O_4 \cdot 1.1 H_2O$: C, 52.41; H, 5.28; N, 8.73. Found: C, 52.18; H, 5.27; N, 9.12.

Example 2

[1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-yl]-methanol

Step A: 1-((S)-2-Benzyloxycarbonylaminoethyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid benzyl ester

To a stirred solution of the product from Step C, Example 1 (0.12 g, 0.32 mmol) in DMF (10 mL) was added potassium carbonate (0.15 g, 1.05 mmol) followed by benzyl 2-bromoacetate (0.08 g, 0.48 mmol) at room temperature and the mixture was heated at 70 °C for 20 h. A saturated aqueous solution of ammonium chloride (20 mL) was added followed by ethyl acetate (50 mL). The organic layer was separated and the aqueous was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried and evaporated to a residue, which was purified by chromatography (silica, 50% ethyl acetate in hexane) to give a solid (0.11 g, 71%): mp 140-141 °C; MS (ES) m/z 484 (M^+).

Step B: [(S)-2-(7-Hydroxymethyl-furo[2,3-*g*]indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

To a stirred solution of the product from Step A (0.13 g, 0.27 mmol) in ethanol (10 mL) was added calcium chloride (0.06 g, 0.54 mmol) in THF (2 mL) followed by sodium borohydride (0.04 g, 1.07 mmol) at 0 °C and the mixture was stirred at room temperature for 20 h. The reaction mixture was evaporated to a residue and a saturated aqueous solution of ammonium chloride (20 mL) was added followed by ethyl acetate (50 mL). The organic layer was separated and the aqueous was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried and evaporated to a residue, which was purified by chromatography (silica, 50% ethyl acetate in hexane) to give an oil (0.05 g, 49%); MS (ES) m/z 380 (M^+).

Step C: [1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-yl]-methanol

A solution of the product from Step B (0.05 g, 0.13 mmol) in ethanol (5 mL) was treated as described in Step E of Example 1, but using a mixture of 9% methanol:1% ammonium hydroxide in dichloromethane as chromatography solvent to give the free base as an amorphous solid (0.032 g): mp 110-112 °C; MS (ES) m/z 246 (M^+); 1H NMR (DMSO- d_6) δ 8.16 (s, 1H), 7.62 (d, 1H, $J = 9.2$ Hz), 7.41 (d, 1H, $J = 9.2$ Hz), 6.49 (s, 1.7H), 4.65 (m, 3H), 4.55 (m, 1H), 3.53 (m, 1H), 1.03 (d, 3H, $J = 6.4$ Hz). Analysis. Calculated for $C_{13}H_{18}N_3O_2$: C, 62.29; H, 6.27; N, 16.76. Found: C, 62.25; H, 6.09; N, 16.73.

Example 3**1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid amide****Step A: 1-((S)-2-Benzoyloxycarbonylaminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid**

To a solution of the product of Step A, Example 2 (0.15 g, 0.31 mmol) in ethanol (10 mL) was added lithium hydroxide (0.026 g, 0.62 mmol) in water (1 mL) and stirred at room temperature for 16 h. The reaction mixture was evaporated to a residue and a saturated aqueous solution of ammonium chloride (20 mL) was added followed by the addition of phosphoric acid (1 M) until the solution was neutral. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined extracts were washed with brine (30 mL), dried and evaporated. The residue was purified by chromatography (silica, dichloromethane, 5% methanol in dichloromethane, 10% methanol in dichloromethane) to give an oil (0.12 g, 98%): MS (ES) m/z 394 (M^+); 1H NMR (CD_3OD) δ 7.91 (s, 1H), 7.81 (s, 1H), 7.58 (d, 1H, $J = 8.8$ Hz), 7.25 (d, 1H, $J = 8.8$ Hz), 7.14-7.02 (m, 5H), 4.81 (s, 2H), 4.49-4.42 (m, 2H), 4.17 (m, 1H), 1.18 (d, 3H, $J = 6.8$ Hz).

Step B: [(S)-2-(7-Carbamoyl-furo[2,3-*g*]indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

To a stirred solution of the product from Step A (0.17 g, 0.43 mmol) in DMF (5 mL) was added 1-hydroxy-benzotriazole hydrate (0.029 g, 0.21 mmol) and 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 g, 0.65 mmol) followed by a solution of ammonia in dioxane (0.5 M, 1.72 mL, 0.86 mmol). After 18 h, a saturated aqueous solution of ammonium chloride (20 mL) added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine, dried and
5 evaporated. The residue was purified by chromatography (silica, dichloromethane, 5% methanol in dichloromethane) to give an oil (0.14 g, 83%): MS (ES) m/z 393(M^+); 1H NMR ($CDCl_3$) δ 8.20 (brs, 1H), 8.04 (s, 1H), 8.01(s, 1H), 7.69 (d, 1H, $J = 8.0$ Hz), 7.32–7.23 (m, 6H), 6.76 (brs, 2H), 5.03 (m, 2H), 4.63 (m, 2H), 4.40 (m, 1H), 1.16 (d, 3H, $J = 8.0$ Hz).

10 Step C: 1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid amide

A solution of the product from Step B (0.098 g, 0.25 mmol) in ethanol (10 mL) was treated as described in Step E of Example 1, but without chromatography, to give the fumarate salt (0.065 g): mp 170-172 °C; MS (ES) m/z 259 (M^+); 1H NMR ($DMSO-d_6$) δ 8.29(s, 1H), 8.21(s, 1H), 7.83(d, 1H, $J = 8.8$ Hz), 7.67 (brs, 1H), 7.47 (d, 1H, $J = 8.8$ Hz),
15 6.48 (s, 1H), 4.71-4.54 (m, 2H), 3.54 (m, 1H), 1.06 (d, 3H, $J = 6.4$ Hz). Analysis. Calculated for $C_{13}H_{14}N_4O_2 \cdot 1.0 C_4H_4O_4 \cdot 0.2 H_2O$. C, 54.02; H, 4.91; N, 14.82. Found: C, 54.06; H, 5.25; N, 15.09.

Example 4

20 **1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid methyl amide fumarate**

This compound was prepared by following a procedure similar to that described in Example
25 3, but replacing ammonia in dioxane with methylamine hydrochloride in Step B to give the fumarate salt: mp 180-182 °C; MS (ES) m/z 273 (M^+); 1H NMR ($DMSO-d_6$) δ 8.75(q, 1H, $J = 4.4$ Hz), 8.21 (s, 1H), 8.19 (s, 1H), 7.82 (d, 1H $J = 8.8$ Hz), 7.45 (d, 1H, $J = 8.8$ Hz), 6.48 (s, 1H), 4.66-4.50 (m, 2H), 3.54 (m, 1H), 2.85 (d, 3H, $J = 4.4$ Hz), 1.04 (d, 3H, $J = 6.4$ Hz). Analysis. Calculated for $C_{14}H_{16}N_4O_2 \cdot 0.5 C_4H_4O_4 \cdot 1.0 H_2O$: C, 55.17; H, 5.79; N, 16.08.
30 Found: C, 54.86; H, 5.71; N, 15.69.

Example 5**1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (2-hydroxyethyl)-amide fumarate**

5
Step A: [(S)-2-[7-(2-Hydroxyethylcarbamoyl)-furo[2,3-*g*]indazol-1-yl]-1-methylethyl]-carbamic acid benzyl ester

A stirred solution of the product from Step A, Example 2 (0.44 g, 0.91 mmol) in ethanolamine was heated at 80 °C for 8 h. A saturated aqueous solution of ammonium
10 chloride (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine, dried and evaporated to a residue, which was purified by chromatography (silica, 60% ethyl acetate in hexane) to give an oil (0.23 g, 57%): MS (ES) m/z 437(M^+); 1H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.69 (d, 1H, $J = 8.0$ Hz), 7.22–7.30 (m, 7H), 5.30 (brs, 1H), 5.03 (m, 2H), 4.63 (m, 1H), 4.40 (m, 1H), 4.15 (m, 1H),
15 3.85 (m, 2H), 3.65 (m, 2H), 1.26 (d, 3H, $J = 8.0$ Hz).

Step B: 1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (2-hydroxyethyl)-amide

A solution of the product from Step A (0.23 g, 0.52 mmol) in ethanol (10 mL) was
20 treated as described in Step C of Example 3 to give the fumarate salt as an amorphous solid (0.14 g): MS (ES) m/z 303 (M^+); 1H NMR ($DMSO-d_6$) δ 8.78 (t, 1H, $J = 6.6$ Hz), 8.29 (s, 1H), 8.23 (1H), 7.83 (d, 1H, $J = 8.8$ Hz), 7.47 (d, 1H $J = 8.8$ Hz), 6.49 (s, 1H), 4.70–4.74 (m, 2H), 3.54–3.61 (m, 3H), 3.37–3.41 (m, 2H), 1.06 (d, 3H, $J = 6.6$ Hz). Analysis. Calculated for $C_{15}H_{18}N_4O_3 \cdot 1.0 C_4H_4O_4 \cdot 1.75 H_2O$: C, 50.72; H, 5.71; N, 12.45. Found: C, 50.37; H,
25 5.68; N, 12.85.

Example 6**1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid [2-(3*H*-imidazol-4-yl)-ethyl]-amide fumarate**

5 This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with histamine to give the fumarate salt: mp 201-203 °C; MS (ES) m/z 353 (M^+); 1H NMR (DMSO- d_6) δ 8.95 (t, 1H, $J = 6.6$ Hz), 8.29 (s, 1H), 8.24 (s, 1H), 7.84 (d, 1H, $J = 8.8$ Hz), 7.56 (s, 1H), 7.48 (d, 1H, $J = 8.8$ Hz), 6.86 (s, 1H), 6.52 (s, 2H), 4.65-4.76 (m, 2H), 3.58 (m, 1H), 3.53-3.56 (m, 2H), 2.81 (t, 2H, $J = 7.2$ Hz), 1.08 (d, 3H, $J = 6.4$ Hz). Analysis. Calculated for $C_{18}H_{20}N_6O_2 \cdot 1.3 C_4H_4O_4 \cdot 1.3 H_2O$: C, 52.90; H, 5.32; N, 15.96. Found: C, 52.65; H, 5.33; N, 16.19.

Example 7**1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide**

15 This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with 4-(2-aminoethyl)morpholine to give the fumarate salt as an amorphous solid: MS (ES) m/z 373 (M^+); 1H NMR (DMSO- d_6) δ 8.81(t, 1H $J = 6.6$ Hz), 8.34 (s, 1H), 8.24 (s, 1H), 7.99 (d, 1H $J = 8.8$ Hz), 7.51 (d, 1H, $J = 8.8$ Hz), 6.55 (s, 4H), 4.65-4.84 (m, 2H), 3.58 (m, 1H), 3.53-3.56 (m, 5H), 3.45 (m, 2H), 1.06 (d, 3H, $J = 6.4$ Hz).

Example 8**1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (2-methoxyethyl)-amide**

25 ~~This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with 2-methoxyethylamine to give, after deprotection, the fumarate salt:~~ mp 75-76 °C; MS (ES) m/z 276 (M^+); 1H NMR (DMSO- d_6) δ 10.5 (1H, brs), 8.92 (1H, t, $J = 5.2$ Hz), 8.41 (1H, s), 8.31 (1H, s), 7.92 (1H, d, $J = 8.8$ Hz), 7.56 (1H, d, $J + 8.8$ Hz), 6.61 (3H, s), 4.91-4.71 (2H, m), 3.75 (1H, m), 3.35 (3H, s), 1.16

(3H, d, $J = 11.2$ Hz). Analysis. Calculated for $C_{16}H_{20}N_4O_3 \cdot 1.5 C_4H_4O_4 \cdot 0.5 H_2O$: C, 52.90; H, 5.45; N, 11.22. Found: C, 52.71; H, 5.75; N, 11.05.

Example 9

1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (2-hydroxypropyl)-amide

This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with 1-aminopropan-2-ol to give, after deprotection, the fumarate salt: mp 190-191 °C; MS (ES) m/z 317 (M^+); 1H NMR (DMSO- d_6) δ 8.65 (1H, t, $J = 2.6$ Hz), 8.28 (1H, s), 8.23 (1H, s), 7.85 (1H, d, $J = 9.2$ Hz), 7.50 (1H, d, $J = 9.2$ Hz), 6.61 (1H, s), 4.70-4.54 (2H, m), 3.83 (1H, m), 3.54 (1H, m), 3.32-3.24 (2H, m), 1.11 (3H, d, $J = 6.4$ Hz), 1.05 (3H, d, $J = 6.4$ Hz). Analysis. Calculated for $C_{16}H_{20}N_4O_3 \cdot 0.7 C_4H_4O_4$: C, 56.79; H, 5.78; N, 14.09. Found: C, 56.42; H, 5.79; N, 14.39.

Example 10

1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (1-hydroxy-cyclopropylmethyl)-amide

This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with 1-aminomethyl-cyclopropanol to give, after deprotection, the fumarate salt: mp 77-79 °C; LC/MS m/z 329 [$M+H$] $^+$; 1H NMR (D_2O) δ 8.12 (d, $J = 1.8$ Hz, 1H), 7.74 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.68 (s, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 6.62 (s, 2H), 4.67 (m, 2H), 3.89 (m, $J = 6.0$ Hz, 1H), 3.52 (s, 2H), 1.23 (d, $J = 6.6$ Hz, 3H), 0.74 (m, 2H), 0.67 (m, 2H). Analysis. Calculated for $C_{17}H_{20}N_4O_3 \cdot C_4H_4O_4 \cdot 1.5 H_2O \cdot 0.5 CH_4O$: C, 52.38; H, 5.74; N, 10.86. Found: C, 52.27; H, 5.38; N, 10.89.

Example 11**1-((*S*)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (3-hydroxy-2,2-dimethyl-propyl)-amide**

This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with 3-amino-2,2-dimethylpropanol to give, after deprotection, the fumarate salt: mp 103 °C; LC/MS *m/z* 345 [M+H]⁺; ¹H NMR (D₂O): δ 8.12 (s, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.65 (s, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.65 (s, 2.8 H), 4.67 (m, 2H), 3.91 (s, 1H), 3.34 (s, 2H), 3.29 (s, 2H), 3.26 (s, 2H), 1.24 (d, *J* = 7.2 Hz, 3H) 0.90 (s, 6H). Analysis. Calculated for C₁₈H₂₄N₄O₃ · 1.5 C₄H₄O₄ · 0.5 H₂O · 0.5 CH₄O: C, 54.14; H, 6.12; N, 10.31. Found: C, 54.10; H, 6.02; N, 10.47.

Example 12**1-((*S*)-2-Amino-propyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid (3-acetylaminopropyl)-amide**

This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with *N*-(3-aminopropyl)-acetamide to give, after deprotection, the fumarate salt: mp 81 °C; LC/MS *m/z* 358 [M+H]⁺; ¹H NMR (D₂O, 600 MHz): δ 8.22 (s, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.78 (s, 1H), 7.46 (dd, *J* = 9.0, 0.6 Hz, 1H), 6.69 (s, 2H), 4.78 (m, 2H), 4.00 (m, 1H), 3.47 (t, *J* = 6.6 Hz, 2H), 3.29 (t, *J* = 6.6 Hz, 2H), 1.98 (s, 3H), 1.86 (hept, *J* = 6.6 Hz, 2H), 1.32 (d, *J* = 7.2 Hz, 3H). Analysis. Calculated for C₁₈H₂₃N₅O₃ · 1.25 C₄H₄O₄ · H₂O: C, 53.07; H, 5.81; N, 13.46. Found: C, 52.90; H, 5.65; N, 13.43.

Example 13**1-((*S*)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazole-7-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide**

This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with 1-(3-aminopropyl)-pyrrolidin-2-one to give, after deprotection, the fumarate salt: mp 82 °C; LC/MS *m/z* 384 [M+H]⁺; ¹H NMR (D₂O): δ 8.26 (s, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.81 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 6.78 (s, 3.4 H),

4.82 (m, 2H), 4.05 (m, 1H), 3.57 (t, J = 7.2 Hz, 2H), 3.47 (t, J = 7.2 Hz, 2H), 3.43 (t, J = 7.2 Hz, 2H), 2.45 (t, J = 7.8 Hz, 2H), 2.07 (m, 2H), 1.96 (m, 2H), 1.36 (d, J = 6.6 Hz, 3H).

Analysis. Calculated for $C_{20}H_{25}N_5O_3 \cdot 1.8 C_4H_4O_4 \cdot 0.5 H_2O$: C, 54.08; H, 5.53; N, 11.43.

Found: C, 54.03; H, 5.58; N, 11.43.

5

Example 14

1-((S)-2-Aminopropyl)-1H-furo[2,3-g]indazole-7-carboxylic acid (5-methyl-furan-2-ylmethyl)amide

This compound was prepared by following a procedure similar to that described in Example 5, but replacing ethanolamine in Step A with (5-methyl-furan-2-yl)-methylamine to give, after deprotection, the fumarate salt: mp 118-120 °C; LC/MS m/z 353 [M+H]⁺; ¹H NMR (D₂O): δ 8.12 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 0.6 Hz, 1H), 7.33 (dd, J = 9.0, 0.6 Hz, 1H), 6.65 (s, 2.2H), 6.27 (d, J = 3.0 Hz, 1H), 6.02 (d, J = 1.8 Hz, 1H), 4.67 (t, J = 6.6 Hz, 2H), 4.67 (t, J = 6.6 Hz, 2H), 4.50 (s, 2H), 3.92 (m, 1H), 2.24 (s, 3H), 1.27 (d, J = 6.6 Hz, 3H). Analysis. Calculated for $C_{19}H_{20}N_4O_3 \cdot 1.25 C_4H_4O_4 \cdot H_2O$: C, 55.92; H, 5.28; N, 10.87. Found: C, 56.19; H, 5.26; N, 10.83.

15

Example 15

(S)-1-Methyl-2-[7-(3-methyl-1,2,4-oxadiazol-5-yl)-furo[2,3-g]indazol-1-yl]-ethylamine

Step A: 1-((S)-2-Aminopropyl)-1H-furo[2,3-g]indazole-7-carboxylic acid methyl ester

To a 50 mL round bottom flask containing NMP (20 mL), methyl bromoacetate (0.35 g 2.3 mmol), and [2-(7-formyl-6-hydroxy-indazol-1-yl)-1-methyl-ethyl]-carbamic acid benzyl ester (0.751 g, 2.1 mmol) was added K₂CO₃ (1.4 g, 10 mmol). This mixture was heated to 90 °C for 16 h, then allowed to cool to 23 °C, decanted into a saturated aqueous NaHCO₃ solution (50 mL), and extracted with ethyl acetate (2 x 20 mL). The combined extracts were dried (Na₂SO₄), filtered and ~~concentrated~~ ~~The crude~~ product was purified by chromatography (silica gel, hexanes: ethyl acetate gradient, 3:1 to 1:1) to provide an oil: LC/MS m/z 408 [M+H]⁺; ¹H NMR (D₂O): δ 8.19 (s, 1H), 8.06 (s, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.30 (bm, 4H), 5.15 (d, 1H), 5.08 (dd, 2H), 4.8 (m, 1H), 4.6 (m, 1H), 4.29 (m, 1H), 4.01 (s, 3H), 1.19 (d, J = 6.6 Hz, 3H).

30

Step B: (*S*)-1-Methyl-2-[7-(3-methyl-1,2,4-oxadiazol-5-yl)-furo[2,3-*g*]indazol-1-yl]-ethylamine fumarate

To a 50 mL round bottom flask containing THF (5 mL), molecular sieves (0.80 g), sodium hydride (0.040 g, 1.0 mmol; 60 % in mineral oil, washed with hexanes) and acetamide oxime (0.07 g, 1.0 mmol). This mixture was heated to 50 °C for 1 h. The product from Step A (0.20 g, 0.50 mmol) was added and the mixture heated at reflux temperature for 2.5 h, then allowed to cool to 23 °C, decanted into a saturated aqueous NaHCO₃ solution (50 mL), and extracted with dichloromethane (2 x 20 mL). The combined extracts were washed with a saturated aqueous NaHCO₃ solution (50 mL), dried (Na₂SO₄), filtered and concentrated. The crude product was purified by chromatography (silica gel, methanol: dichloromethane gradient, 4% to 8%) to furnish the free base (0.049 g, 32%). Fumaric acid (0.019 g, 0.16 mmol) was added to a solution of the free base in methanol (3 mL) concentration of the mixture provided the salt: mp 187-9 °C; LC/MS *m/z* 298 [M+H]⁺; ¹H NMR (D₂O): δ 7.98 (d, *J* = 3.0 Hz, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.52 (s, 2.4H), 4.58 (m, 2H), 3.83 (m, 1H), 2.27 (s, 3H), 1.19 (d, *J* = 6.6 Hz, 3H). Analysis. Calculated for C₁₅H₁₅N₅O₂ · 1.2 C₄H₄O₄ · 0.7 H₂O: C, 52.94; H, 4.76; N, 15.59. Found: C, 53.07; H, 4.71; N, 15.61.

Example 16

2-[1-((*S*)-2-Amino-propyl)-1*H*-furo[2,3-*g*]indazol-7-yl]-*N*-methyl-acetamide

Step A: [(*S*)-2-(7-Cyanomethyl-furo[2,3-*g*]indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

A solution of the product from Example 2, Step B (0.55 g, 1.45 mmol) in dichloromethane (20 mL) was cooled (ice bath), thionyl chloride (0.16 mL, 2.18 mmol) was added, and the mixture was stirred for thirty minutes. The reaction mixture was evaporated to a residue which was dissolved in dichloromethane (20 mL) and evaporated. A solution of sodium cyanide (0.29 g, 5.8 mmol) in DMSO (10 mL) was added to this residue and the mixture was stirred at room temperature for one hour. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was extracted with ethyl acetate (3 x 100 mL). The

combined extracts were washed with saturated aqueous sodium bicarbonate (2 x 150 mL), dried (MgSO₄) and evaporated to a tan solid (0.49 g, 87%): LC/MS m/z 389 [M+H]⁺.

Step B: [1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-yl]-acetic acid methyl ester

The product from Step A (0.48 g, 1.24 mmol) was added to double distilled 20% aqueous hydrochloric acid (5 mL) and heated at 90 °C for one hour and evaporated to a residue, which was treated with dry methanolic hydrochloric acid (0.5 N, 5 mL) at room temperature overnight. The reaction was evaporated to give the methyl ester (0.25 g, 61%): LC/MS m/z 288 [M+H]⁺.

Step C: 2-[1-((S)-2-Amino-propyl)-1*H*-furo[2,3-*g*]indazol-7-yl]-*N*-methyl-acetamide

The product from Step B (0.25 g, 0.77 mmol) was combined with 2 M methanolic methylamine (10 mL, 20 mmol) and the mixture was stirred at room temperature overnight.

The reaction mixture was evaporated and the residue purified by reversed phase chromatography (gradient, water/acetonitrile with 0.1 % TFA). Evaporation of selected fractions gave an oil (0.15 g; LC/MS 287 m/z) that was treated with methanolic hydrochloric acid (0.5 N, 5 mL) and evaporated to give the methyl amide as an amorphous solid (0.15 g, 60%): LC/MS m/z 287 [M+H]⁺; ¹H NMR (CD₃OD) δ 8.167 (s, 1H), 7.65 and 7.39 (ABq, 2H, J = 9Hz), 7.22 (s, 1H), 4.80 (d, 2H, J = 6Hz), 3.97 (m, 1H, J = 6Hz, J = 7Hz), 3.85 (s, 2H), 2.81 (s, 3H), 1.34 (d, 3H, 7Hz). Analysis. Calculated for C₁₅H₁₈N₄O₂ · 2 HCl · 1.2 H₂O: C, 52.31; H, 6.26; N, 16.27. Found: C, 52.61; H, 6.12; N, 15.93.

Example 17

***N*-[1-((S)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-ylmethyl]-nicotinamide**

Step A: [(S)-2-(7-Azidomethyl-furo[2,3-*g*]indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

A suspension of the product from Example 3, Step B (2.80 g, 7.39 mmol) in dichloromethane (30 mL) was cooled (ice bath), thionyl chloride (0.81 mL, 11.1 mmol) was added and the mixture was stirred for 30 minutes. During the reaction the white suspension

dissolved to a yellow solution and then became a white suspension. The reaction was evaporated. The residue was treated with a solution of sodium azide (5 eq, 37 mmol, 2.4 g) in DMSO (40 mL, heated at 70 °C to dissolve) with stirring and let cool to room temperature for 20 minutes. The reaction was quenched with saturated aqueous sodium bicarbonate (100 mL) and extracted with dichloromethane (200 mL). The organic layer was washed with brine (100 mL), dried (MgSO₄) and evaporated to give a yellow oil, 2.84 g. This residue was purified by chromatography (silica gel, hexane/ethyl acetate gradient) to give a colorless waxy residue, 2.45 g (82 %): LC/MS m/z 405 [M+H]⁺.

Step B: [(S)-2-(7-Aminomethyl-furo[2,3-g]indazol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

A solution of the product from Step A (1.28 g, 3.17 mmol) in THF (25 mL) was stirred with polymer supported triphenylphosphine (4 eq, 3 mmol/g, 12.7 mmol, 4.23 g) at 50 °C for 2 hours. Water (2.5 mL) was added and the mixture was stirred for another hour; more water (5 mL) was added and the reaction mixture was filtered. The solids were washed well with THF and the filtrate was evaporated to a residue which was dried under a vacuum to give a foam (1.10 g, 92 %): LC/MS m/z 379 [M+H]⁺.

Step C: [(S)-1-Methyl-2-(7-[(pyridine-3-carbonyl)-amino]-methyl)-furo[2,3-g]indazol-1-yl)-ethyl]-carbamic acid benzyl ester

To a solution of the product from Step B (0.32 g, 0.847 mmol) in THF (20 mL) was added polymer supported di-isopropyl ethyl amine (3.86 mmol/g, 0.44 g, 1.69 mmol, 2 eq); this suspension was cooled (ice bath) and nicotinoyl chloride (0.15 g, 0.847 mmol) was added. The ice bath was removed and mixture was stirred for one hour, additional nicotinoyl chloride (50 mg) was added and the mixture was stirred at room temperature overnight. Triethylamine was added and after stirring for 10 min saturated aqueous sodium bicarbonate (150 mL) was added. This mixture was extracted with ethyl acetate (2 x 100 mL). The combined extracts were dried (MgSO₄) and evaporated to an oil which was purified by chromatography (silica gel, hexane/ethyl acetate gradient) to give a solid (0.16 g, 39 %): LC/MS m/z 484 [M+H]⁺.

Step D: *N*-[1-((*S*)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-ylmethyl]-nicotinamide

To a solution of the product from Step C (0.16 g, 0.33 mmol) in methanol (20 mL) was added 10% Palladium on carbon (20 mg) and this mixture was stirred under an atmosphere of hydrogen at room temperature for two days. The reaction mixture was filtered and the filtrate evaporated to give a colorless oil (0.10 g, 87%): LC/MS *m/z* 350 [M+H]⁺; ¹H NMR (CD₃OD) δ 9.052 (s, 1H), 8.70 (m, 1H), 8.31 (m, 1H), 8.08 (s, 1H), 7.62 and 7.36 (ABq, J = 9Hz, 2H), 7.56 (m, 1H), 4.50 (overlapping m and s, 4H), 3.47 (m, 1H), 1.08 (d, 3H).

Example 18

1-[1-((*S*)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-ylmethyl]-3-ethylurea

Step A: ((*S*)-2-{7-[(3-Ethylureido)-methyl]-furo[2,3-*g*]indazol-1-yl}-1-methylethyl)-carbamic acid benzyl ester

To a solution of the product from Example 17, Step B (0.20 g, 0.53 mmol) in THF (4 mL) was added polymer supported di-isopropylamine (1.5 eq, 0.79 mmol, 0.22 g) and ethyl isocyanate (0.042 mL, 0.52 mmol); this mixture was stirred at room temperature for three hours followed by the addition of methanol (5 mL). Dichloromethane (15 mL) was added and the mixture was filtered, evaporation of the filtrate gave a solid (0.19 g) which was purified by chromatography (silica gel, hexane/ethyl acetate gradient) to give a white solid (0.14 g, 59 %): LC/MS *m/z* 450 [M+H]⁺.

Step B: 1-[1-((*S*)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-ylmethyl]-3-ethylurea

Reaction of the product from Step A in a manner similar to that described in Example 17,

Step D gave a colorless oil (98-mg): LC/MS-*m/z* 316 [M+H]⁺; ¹H NMR (CD₃OD) δ 7.97 (d, 1H), 7.49 and 7.23 (ABq, J = 9 Hz, 2H), 7.32 (s, 1H), 4.43 (s, 2H), 4.41 (m, 2H), 3.41 (m, J = 6 Hz 1H), 3.08 (q, J = 7 Hz, 2H), 1.01 (overlapping d and t, J = 6Hz and 7Hz, 6H).

Example 19

***N*-(4-{[1-((*S*)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-ylmethyl]-sulfamoyl}-phenyl)-acetamide**

Step A: ((*S*)-2-{7-[(4-Acetylamino-benzenesulfonylamino)-methyl]-furo[2,3-*g*]indazol-1-yl}-1-methyl-ethyl)-carbamic acid benzyl ester

A solution of the product from Example 17, Step B (0.32 g, 0.85 mmol) in THF (10 mL) containing triethylamine (3.39 mmol, 0.47 mL) was cooled (ice bath) and *N*-acetylsulfanilyl chloride (0.20 g, 0.85 mmol) was added followed by stirring for one hour. The reaction mixture was warmed to room temperature, water (1 mL) was added, and stirring continued until all the solids dissolved. Saturated aqueous sodium bicarbonate (150 mL) was added and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed with brine (100 mL), dried (MgSO₄) and evaporated to a residue which was purified by chromatography (silica gel, hexane/ethyl acetate gradient) to give an amorphous solid (0.32 g, 66 %): LC/MS *m/z* 576 [M+H]⁺.

Step B: *N*-(4-{[1-((*S*)-2-Aminopropyl)-1*H*-furo[2,3-*g*]indazol-7-ylmethyl]-sulfamoyl}-phenyl)-acetamide

Reaction of the product from Step A in a manner similar to that described in Example 17, Step D gave a colorless solid (0.23 g, 94%): mp 80-85 °C; LC/MS *m/z* 442 [M+H]⁺; ¹H NMR (CD₃OD) δ 7.93 (s, 1H), 7.53 and 7.32 (ABq, 4H, 7Hz), 7.45 and 7.08 (ABq, 2H, 9Hz), 6.79 (s, 1H), 4.28 (overlapping m and s, 4H), 3.29 (m, 1H, 6Hz), 1.94 (s, 3H), 0.97 (d, 3H, 6Hz) Analysis. Calculated for C₂₁H₂₃N₅O₄S · 0.4 H₂O: C, 56.21; H, 5.35; N, 15.61. Found: C, 56.50; H, 5.31; N, 15.25.

Example 20

(*S*)-1-Methyl-2-[7-(4-pyridin-2-yl-piperazin-1-ylmethyl)-furo[2,3-*g*]indazol-1-yl]-ethylamine

Step A: {(*S*)-1-Methyl-2-[7-(4-pyridin-2-yl-piperazin-1-ylmethyl)-furo[2,3-*g*]indazol-1-yl]-ethyl}-carbamic acid benzyl ester

A solution of the product from Example 3, Step B (0.18 g, 0.475 mmol) in dichloromethane (20 mL) was cooled (ice bath) and thionyl chloride (0.052 mL, 0.71 mmol) added. The mixture was stirred for 30 min and then evaporated to a residue which was dissolved in dichloromethane (20 mL); this solution was evaporated and the residue dried under a vacuum. The residue was dissolved in dichloromethane (20 mL) and 1-(2-pyridyl)piperazine (0.5 mL, 3.4 mmol) was added, and the mixture was stirred at room temperature for one hour at which point additional 1-(2-pyridyl)piperazine (0.9 mL) was added. Solvent was removed by evaporation (45 °C) and THF (10 mL) was added, followed by heating the mixture at reflux temperature for one hour. This reaction mixture was evaporated and the residue dissolved in methanol (25 mL) and triethylamine (1.5 mL) followed by evaporation of this mixture to a residue which was purified by chromatography (silica gel, hexane/ethyl acetate) to give a foamy solid (0.21 g, 84 %): LC/MS m/z 525 [M+H]⁺.

Step B: (*S*)-1-Methyl-2-[7-(4-pyridin-2-yl-piperazin-1-ylmethyl)-furo[2,3-*g*]indazol-1-yl]-ethylamine

Reaction of the product from Step A in a manner similar to that described in Example 17, Step D gave a colorless oil (0.15 g, 96 %): LC/MS m/z 391 [M+H]⁺; ¹H NMR (CD₃OD) δ 7.97 (s, 2H), 7.52 (d, J = 8 Hz, 1H), 7.43 (m, 1H), 7.62 and 6.69 (ABq, J = 9 Hz, 2H), 7.18 (s, 1H), 6.56 (m, 1H), 4.39 (m, 2H), 3.75 (s, 2H), 3.44 (m, 4H), 3.36 (m, 1H), 2.61 (br, 4H), 0.98 (d, J = 7 Hz, 3H). Analysis. Calculated for C₂₂H₂₆N₆O · 0.6 H₂O: C, 65.85; H, 6.83; N, 20.94. Found: C, 65.95; H, 6.85; N, 20.58.

The compounds of the present invention can be used to lower and control IOP including IOP associated with normotension glaucoma, ocular hypertension, and glaucoma in warm blooded animals including humans and other mammals. Since the treatment of glaucoma is preferably with ~~compounds that do not enter the CNS~~, relatively polar compounds that are 5-HT₂ agonists are of particular interest. The compounds are preferably formulated in pharmaceutical compositions which are preferably suitable for topical delivery to the eye of the patient.

The compounds of this invention, Formula A, can be incorporated into various types of pharmaceutical compositions, such as ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an implant). The compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined
5 with ophthalmologically acceptable preservatives, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound.
10 Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active
15 ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

20 The compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled
25 clinician.

The compounds can also be used in combination with other agents for treating glaucoma, such as, but not limited to, β -blockers (e.g., timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide), α_1 antagonists (e.g., nipradolol), α_2 agonists (e.g. iopidine and brimonidine),
30 miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travoprost,

unoprostone, and compounds set forth in U.S. Patent Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444, "hypotensive lipids" (e.g., bimatoprost and compounds set forth in 5,352,708), and neuroprotectants (e.g., compounds from U.S. Patent No. 4,690,931, particularly eliprodil and R-eliprodil, as set forth in a pending application U.S.S.N. 60/203,350, and appropriate
5 compounds from WO 94/13275, including memantine.

In the formulas described above, the alkyl group can be straight-chain, branched or cyclic and the like. Halogen includes Cl, Br, F, or I. Alkoxy is understood as an alkyl group bonded through an oxygen atom.

The compounds of the present invention preferably function as 5-HT₂ agonists and
10 preferably do not enter the CNS. Compounds having the ability to be a 5-HT₂ agonist are beneficial for controlling IOP as well as the treatment of glaucoma as shown in International Published Patent Application No. WO 00/16761, incorporated in its entirety by reference herein.

The compounds of the present invention preferably provide increased chemical stability
15 and preferably achieve the desired level of therapeutic activity which includes a lowering or controlling of IOP.

The compounds of the present invention can be used in controlling or lowering IOP in warm blooded animals including humans. Preferably, an effective amount of the compound is administered to the patient such that the IOP is controlled or lowered to acceptable levels.

20 Furthermore, the compounds of the present invention can be used to treat glaucoma in warm blooded animals, including humans, by administering an effective amount of the compound to a patient in need of such treatment to treat the glaucoma. Pharmaceutically acceptable amounts of the compounds of the present invention will be readily understood by those skilled in the art to mean amounts sufficient to effect the desired therapy without toxicity or other deleterious
25 effects on the patients' health. Examples of such amounts include without limitation those amounts shown in the Examples.

Another embodiment of the present invention is a method of activating or binding serotonin receptors, comprising administering an effective amount of at least one compound of the present invention to a patient using an amount effective to activate or bind serotonin

receptors, wherein such amount includes, but is not limited to, the dosage levels described herein.

The procedures described herein in Method 1 can be used to confirm a compound's 5-HT₂ binding affinity.

METHOD 1

5-HT₂ Receptor Binding Assay

To determine the affinities of serotonergic compounds at the 5-HT₂ receptors, their ability to compete for the binding of the agonist radioligand [¹²⁵I]DOI to brain 5-HT₂ receptors is determined as described below with minor modification of the literature procedure [Neuropharmacology, 26, 1803 (1987)]. Aliquots of post mortem rat or human cerebral cortex homogenates (400 µL) dispersed in 50 mM TrisHCl buffer (pH 7.4) are incubated with [¹²⁵I]DOI (80 pM final) in the absence or presence of methiothepin (10 µM final) to define total and non-specific binding, respectively, in a total volume of 0.5 mL. The assay mixture is incubated for 1 hour at 23°C in polypropylene tubes and the assays terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Test compounds (at different concentrations) are substituted for methiothepin. Filter-bound radioactivity is determined by scintillation spectrometry on a beta counter. The data are analyzed using a non-linear, iterative curve-fitting computer program [Trends Pharmacol. Sci., 16, 413 (1995)] to determine the compound affinity parameter. The concentration of the compound needed to inhibit the [¹²⁵I]DOI binding by 50% of the maximum is termed the IC₅₀ or K_i value.

METHOD 2

5-HT₂ functional Assay: [Ca²⁺]_i Mobilization

The receptor-mediated mobilization on intracellular calcium ([Ca²⁺]_i) was studied using the Fluorescence Imaging Plate Reader (FLIPR) instrument. Rat vascular smooth

muscle cells, A7r5, were grown in a normal media of DMEM / 10% FBS and 10 $\mu\text{g/mL}$ gentamycin. Confluent cell monolayers were trypsinized, pelleted, and re-suspended in normal media. Cells were seeded in a 50 μL volume at a density of 20,000 cells / well in a black wall, 96-well tissue culture plate and grown for 2 days.

5 On the day of the experiment, one vial of FLIPR Calcium Assay Kit dye was re-suspended in 50 mL of a FLIPR buffer consisting of Hank's Balanced Salt Solution (HBSS), 20 mM HEPES, and 2.5 mM probenecid, pH 7.4. Cells were loaded with the calcium-sensitive dye by addition of an equal volume (50 μL) to each well of the 96-well plate and incubated with dye for 1h at 23°C.

10 Typically, test compounds were stored at 25 μM in 50% DMSO/50% Ethanol solvent. Compounds were diluted 1:50 in 20% DMSO/20% Ethanol. For "hit" screening, compounds were further diluted 1:10 in FLIPR buffer and tested at a final concentration of 10 μM . For dose-response experiments, compounds were diluted 1:50 in FLIPR buffer and serially diluted 1:10 to give a 5- or 8- point dose-response curve.

15 The compound plate and cell plate were placed in the FLIPR instrument. At the beginning of an experimental run, a signal test was performed to check the basal fluorescence signal from the dye-loaded cells and the uniformity of the signal across the plate. The basal fluorescence was adjusted between 8000-12000 counts by modifying the exposure time, the camera F-stop, or the laser power. Instrument settings for a typical assay
20 were the following: laser power 0.3-0.6 W, camera F-stop F/2, and exposure time 0.4 sec. An aliquot (25 μL) of the test compound was added to the existing 100 μL dye-loaded cells at a dispensing speed of 50 $\mu\text{L/sec}$. Fluorescence data were collected in real-time at 1.0 sec intervals for the first 60 secs and at 6.0 sec intervals for an additional 120 secs. Responses were measured as peak fluorescence intensity minus basal and where appropriate were
25 expressed as a percentage of a maximum 5-HT-induced response [E_{max} %]. When the compounds were tested as antagonists against 10 μM 5-HT, they were incubated with the cells for 15 minutes prior to the addition of 5-HT.

Using the foregoing methods, 5-HT₂ binding affinities and agonist potential can readily be determined.

30 The above procedures were used to generate the data shown in Table 1.

Table 1
5-HT_{2A} Receptor Binding and Functional Data

Example	5HT_{2A} (rat) IC₅₀, nM	5-HT_{2A} (rat) EC₅₀, nM (E_{max})	E_{max} (%)
1	0.21	63	101
2	0.53	18	86
3	2.3	158	87
4	0.81	54	98
5	3.5	55	94
6	0.66	57	95
7	1.3	109	89
8	2.3	54	94
9	1.5	27	98
10	1.1	15	94
11	1.8	74	76
12	1.4	37	95
13	2.0	72	87
14	0.3	181	94
15	0.9	283	101
16	0.7	28	97
17	3.0	22	95
18	4.1	23	87
19	4.1	131	82
20	----	141	81
5-HT	0.9	56	101

Table 2**IOP Response in Conscious Cynomolgus Monkeys**

<u>Example</u>	Dose, μg	Baseline IOP (mmHg)	Percent IOP Reduction \pm SEM <u>Hours after Dose</u>		
			1	3	6
3	300	32.8	9 \pm 4	23 \pm 4	27 \pm 5
4	300	34.9	13 \pm 3	30 \pm 4	31 \pm 4
11	300	37.8	10 \pm 5	23 \pm 5	26 \pm 5
(R)-DOI	100	31.9	11 \pm 5	25 \pm 3	34 \pm 5

- 5 IOP was determined with an Alcon Pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Eyes were washed with saline after each measurement. After a baseline IOP measurement, test compound was instilled in one 30 μ L aliquot to the right eyes only of nine cynomolgus monkeys. Vehicle was instilled in the right eyes of six additional animals. Subsequent IOP measurements were taken at 1, 3, and 6 hours.

10

The following topical ophthalmic formulations are useful according to the present invention administered 1-4 times per day according to the discretion of a skilled clinician.

Example 21

Ingredients	Amount (wt %)
Compound of Example 4	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

Example 22

<u>Ingredients</u>	Amount (wt %)
Compound of Example 4	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

Example 23

Ingredients	Amount (wt %)
Compound of Example 3	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

5

Example 24

Ingredients	Amount (wt %)
Compound of Example 11	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. For example, it is understood that any of the compounds of the present invention may be formulated in the manner described in any of Examples 21-24. It is
5 intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☒ **BLACK BORDERS**

☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☐ **FADED TEXT OR DRAWING**

☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKEWED/SLANTED IMAGES**

☒ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☐ **GRAY SCALE DOCUMENTS**

☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.